

Breast-conserving treatment for stage I and II cancer

Tumour excision, axillary dissection, peri-operative interstitial irradiation, with or without peri-operative chemotherapy, followed by breast irradiation — the Tygerberg Hospital experience

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Summary

Since 1984 breast-conserving treatment has been the treatment of choice for patients at Tygerberg Hospital with early breast cancer. Peri-operative interstitial brachytherapy in breast cancer is described in detail. In the 221 patients treated (225 breasts), 197 breasts received iridium implants and 26 patients received peri-operative chemotherapy (POPFAC). There were 6 recurrences in treated breasts, 3 within the booster area and 3 outside. There were 5 salvage mastectomies, and 1 patient was treated by excision and radiotherapy. Metastases developed in 27 patients. Two patients underwent mastectomy for severe radiation changes and 7 developed postoperative wound infection after POPFAC. Five patients, who had re-excisions and prolonged seroma formation, developed delayed wound infection after POPFAC. Five patients, who had re-excisions and prolonged seroma formation, developed delayed wound infection. The importance of mammography, patient selection, tumour-free margins and radiation dosage are discussed.

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The results of breast-conserving treatment (BCT) are equivalent to mastectomy in terms of local recurrence, relapse-free survival and overall survival.¹⁻⁴

However, many aspects — optimal method of boosting, optimal radiotherapy dose required, long-term effects of radiotherapy on normal as well as on premalignant breast tissue and the need for routine axillary clearance — are unresolved. Since 1984 the Tygerberg Hospital Breast Clinic has participated in the randomised trial of the European Organisation for Research and Treatment of Cancer (EORTC) on BCT v. mastectomy. Results of this multicentre trial have been reported by the study co-ordinators.⁵

Our methods and the experience gained in BCT are described in detail, with emphasis on peri-operative interstitial radiotherapy about which there have been few reports.

Patients and methods

All patients presenting primarily at this clinic were evaluated and assessed for treatment by both the surgeon (J.v.Z.) and radiotherapist (A.G.S.M.). Similarly, all patients referred after surgery were re-staged before radiotherapy began.

The patient population consisted of 221 patients, treated between February 1984 and December 1987. Of the 225 breasts, 135 were treated primarily at Tygerberg Hospital and 86 were referred postoperatively by private surgeons for radiotherapy.

The age distribution with each diagnosis of cancer in 10-year age groups was: 20-29 years — 7 patients, 30-39 — 50, 40-49 — 54, 50-59 — 42, 60-69 — 49, and 70-74 — 23. At the time of diagnosis of each tumour 115 patients were premenopausal and 109 postmenopausal, the menopausal status of 1 patient was not recorded. The tumours were staged by UICC TNM criteria: 65 had stage I disease and 160 stage II. One hundred and fourteen tumours occurred in the right breast and 107 in the left, a second tumour in the opposite breast occurred in 4 patients. The quadrants involved were: upper-outer 108, lower-outer 31, upper-inner 58, lower-inner 22 and central 6. Three patients had bilateral metachronous and 1 had bilateral synchronous breast carcinoma.

Pre-operative evaluation

Pre-operative evaluation included chest radiography, limited skeletal survey, blood chemistry investigation, full blood count, bone scan and mammography. The diagnosis was confirmed by fine-needle aspiration cytology.⁶ If this modality was unsuccessful, or if a papillary neoplasm was reported, an excision biopsy was performed followed by definitive treatment a week later.

Tumour excision

The skin incision was made directly over the tumour. A small ellipse of skin directly overlying the tumour was excised, minimising flap dissection. In the upper half of the breast, the incision conformed with the lines of Langer and in the lower half a vertical incision, which minimised distortion of the breast, was preferred. The tumour and 1-2 cm of surrounding normal breast tissue was excised. The incision extended down to the pectoralis fascia. It was important to palpate the wound area for any remaining suspect tissue. The specimen was sectioned to determine macroscopically whether all tumour was excised and to measure the tumour diameter. If the borders seemed to be marginal, these areas were re-excised. No attempt was made to approximate the breast tissue by suturing. The wound was closed by a single layer of subcutaneous polyglactin sutures. The wound was drained by a small rubber drain for 4-5 days. To ensure tumour-free margins, patients diagnosed at an outside hospital all underwent re-excision of the biopsy site.

Axillary lymph node dissection

The axillary lymph node dissection was preferably performed through a separate incision, except for tumours situated near

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the axilla, which were excised in continuity with the axillary lymph node dissection. The incision was made anteroposteriorly, crossing the axillary fossa in a downward direction. The pectoralis minor muscle was cut at its origin to facilitate complete removal of the lymph nodes up to the apex of the axilla. During the operation the boundaries of the lower, higher and apical lymph node regions were marked with coloured beads to ensure accurate sectioning of the specimen. The thoracodorsal neurovascular bundle and nerve to the latissimus dorsi were preserved. The skin incision was closed with a single layer of continuous subcutaneous polyglactin sutures. The wound was drained by a suction drain.

Radiotherapy technique

Iridium-192 implant as a booster

We used an afterloading technique to deliver the booster dose of radiation. The target area was determined during surgery. If the excision was macroscopically complete, the target area comprised the tumour diameter plus 1 cm on either side. If there was any doubt about the excision margin, the target area was increased to the tumour diameter plus 2 cm on either side. The distribution and number of wires was determined by the activity of the iridium wire. Templates were used to position and maintain the needles. In single-plane implants the distance between sources was 10 mm. In double-plane implants it varied between 15 mm and 20 mm. We preferred double-plane implants.

With the wound open, the first of two rows of hollow stainless-steel needles was inserted through the tumour bed. The wound was then sutured and the second row of needles inserted. The needles had to be positioned a minimum distance of 10 mm from the skin. The templates and needles were held in position by lead crimps. To remove any tissue debris from the lumen of the hollow needle, a thin solid needle was pushed through it. The sharp end of the needle was cut off, sealing the end. The tumour area was marked on the skin. Thin plastic tubing, 1 mm in diameter, was inserted into each needle, creating a dead space from the needle end to the target area. The iridium wires were loaded 2 days after surgery. A dosage of 10 Gy/d, with a total dose of 25 Gy (calculated on the 85% isodose curve), was given.

Patients referred after tumour excision and axillary lymph node dissection received the booster dose by implant 2 weeks after completion of external beam therapy or 1 week before external irradiation was started.

The rules of the Paris system⁷ were followed when calculating the dose.

External beam booster

Where an implant was not feasible, the booster dose was given by external beam therapy. The treatment was planned with two wedge fields to the tumour bed. A tumour dose of 20 Gy in 10 fractions was given after completion of the irradiation to the whole breast.

External beam therapy technique

The whole breast was treated by external beam therapy 3-4 weeks after surgery. Two tangential fields were used. The limits of the fields were 2 cm above and below the breast. Treatment was planned using wedge or compensating filters and lung corrections were made routinely.

Dosage

A tumour dose of 50 Gy was delivered by cobalt-60 radiation in 25 fractions of 2 Gy tumour dose over 5 weeks. The dosage variation within the treated area was less than 10%.

Technique of treatment planning

Planning was performed with the use of computed tomography (CT). With the patient supine, arms elevated and hands under the head, the upper and lower limits of the breast fields were marked on the skin. A single CT view through the central plane was obtained to delineate the breast and underlying lung for planning purposes.

Internal mammary lymph node irradiation

Seventy-three patients with centrally and medially located tumours received internal mammary irradiation. A given dose (GD) of 50 Gy in 25 fractions of 2 Gy was administered.

Supraclavicular irradiation

Twenty-three patients with apical lymph node or extranodal involvement received supraclavicular irradiation. A GD of 50 Gy in 25 fractions of 2 Gy was administered.

Adjuvant chemotherapy

Fifteen premenopausal lymph node-positive patients received adjuvant cyclophosphamide, methotrexate and 5-fluoro-uracil (CMF) chemotherapy for 6 courses. These patients were part of the EORTC trial.⁵ Twenty-six patients received a single dose of cyclophosphamide, adriamycin and 5-fluoro-uracil (CAF) 24 hours postoperatively. These patients form part of an ongoing EORTC trial.⁸

Pathological examinations

To ensure consistency in pathological reports all material was evaluated by one pathologist. The following features were specifically noted: tumour differentiation; presence and extent of ductal carcinoma *in situ*; presence of tumour on the excision margin; level of nodal involvement; extranodal involvement; and presence of tumour in soft tissue.

Oestrogen and progesterone receptor content were determined according to the method of McGuire *et al.*⁹

Results

The 221 patients were followed up for 5-52 months and 225 breasts were treated. Two patients had undergone mastectomy previously for contralateral breast cancer.

In 139 axillas the lymph nodes were not involved in the disease process. Lymph node involvement was present in 83 axillas: 55 had 1-3 nodes, 22 had 4-9 nodes, and 6 more than 9 nodes involved. In 9 axillas the apical lymph nodes were involved.

In 30 patients the axillary lymph node clearance and tumour excision had to be performed through a single incision. In 3 patients (over 70 years of age with medially located tumours and clinically normal axillas) no axillary lymph node clearance was performed.

One hundred and ninety-seven breasts received iridium implants as booster therapy; 126 of these implants were positioned intra-operatively.

Recurrence

Three patients developed local recurrence within the booster area. On review, 2 had had inadequate excision of the primary tumour, 1 patient having had 2 tumours. Both patients were treated within the first 3 months of the study period. Both underwent salvage mastectomy and subsequently developed

metastatic disease. One has died. The third patient was 28-years-old and her tumour had an extensive intraductal component. Salvage mastectomy was performed for the recurrent tumour, which on pathological examination consisted almost entirely of ductal carcinoma *in situ*. This patient is disease-free at present.

Three patients developed a second tumour outside the booster area. On pathological examination one tumour had no intraductal component and was classified as a true recurrence, the other 2 patients, who had associated intraductal carcinoma, were regarded as having second primary tumours. One of these patients was treated by tumour excision and iridium implant to 30 Gy. Twenty-four months later, she remained free of disease. The remaining 2 patients were treated by mastectomy. One developed metastatic disease and is alive, the other remains free of disease. On review of their original mammograms, 1 patient had microcalcifications, which had been overlooked, in the area where the subsequent tumour developed.

Seven subsequent mastectomies have been performed in this series, 5 for recurrent disease as described above. Two patients with very large breasts had a mastectomy for severe symptomatic radiation changes. One of our patients developed non-related malignant disease of the cervix. She remains free of mammary disease.

Metastases

In total 27 patients developed metastatic disease. Two of these presented simultaneously with metastases and diffuse recurrence within the breast. Both were referred patients, 1 of whom, on review, had had residual macroscopic tumour during surgery for the primary tumour. One of these patients has died, the other has stable disease on chemotherapy. The remaining patients with metastatic disease are free from local recurrence.

Deaths

Nine patients died, 6 of metastatic disease and 3 of unrelated causes. Only 1, already mentioned, had evidence of local recurrence at death.

Wound infection occurring before completion of radiotherapy

Two patients developed infection of the tumour excision wound, 1 of whom had received peri-operative CAF. Four patients developed infection of the axillary wound, 3 had received peri-operative CAF. One patient, who received peri-operative CAF, had infection at both sites. This patient was confused postoperatively and pulled out all her drainage tubes.

Wound infection at the tumour excision scar

This occurred in 5 patients 4 - 8 months after completion of therapy. All developed the infection in a persistent seroma. Four of these had undergone biopsy elsewhere and had re-excision of the tumour site.

Discussion

Pre-operative evaluation

Patient selection

We considered all patients up to 75 years of age for BCT, since patients over 75 years are treated by tumour excision and tamoxifen.⁸ In our experience the elderly patient is as keen to

retain her breast as the young woman. Four of 6 patients with local recurrence were under 40 years of age at the time of diagnosis, which is in accordance with the findings of Recht *et al.*¹⁰ These patients, particularly if a marked degree of carcinoma *in situ* is present, require very careful follow-up. This, however, does not imply that a young woman should not be considered for BCT.¹⁰⁻¹³

Mammography

In all patients considered for BCT, high-quality film mammography is mandatory. With this examination,¹⁴ multiple tumours, diffuse microcalcifications indicative of possible widespread carcinoma *in situ* or infiltrating carcinoma and poorly circumscribed tumours, which may indicate wide infiltration, can be diagnosed. Patients with these features should not be considered for BCT. The local recurrence in 2 of our patients could be attributed directly to poor quality mammography, not observing additional microcalcifications in 1 case and multiple tumours in the other.

Tumour size

We regard a tumour size of 4 cm as the upper limit of suitability for BCT. Larger tumours necessitate more extensive surgery and a larger booster area, resulting in poor cosmesis and increased risk of local recurrence. Patients with inadequate excision have been reported to have only 66% local control opposed to 89% with complete excision.¹⁵

Breast size

Breast size is a relative contraindication to BCT. In our experience only 1 patient had a breast too small for BCT since tumour excision would have removed all her breast tissue. We find very large breasts a more serious problem. There are technical problems associated with radiotherapy, i.e. patient positioning is very difficult and dosage distribution is not homogeneous, leading to unacceptable fibrosis, as experienced in 2 patients. BCT with simultaneous bilateral breast reduction could possibly be considered for these patients, since a mastectomy results in unacceptable postural problems, a fact often ignored by the surgeon.

Surgery

Incision

It is important to make the incision directly over the tumour.¹⁶ Subcutaneous dissection from a circumareolar incision towards a peripherally located tumour is likely to result in an incomplete excision and an increased risk of local recurrence, as experienced in 1 of the referred patients. Large excisions in the upper quadrant often lead to nipple displacement and, if this is anticipated, the areola should be dissected free from the underlying breast tissue even if this necessitates cutting the milk ducts.³ Incisions made along the lines of Langer for lower quadrant tumours, tend to fix the breast against the chest wall. A radial incision avoids this complication. If the lower part of the excision traverses the inframammary fold, a diamond-shaped incision gives extra length to the wound and maintains breast mobility.

Extent

A tumour excision with 1-2 cm surrounding breast tissue, which is our policy, is sufficient. Quadrantectomy and segmental resections are no longer justified because cosmesis is poor and local control and survival are not superior to lesser surgery and adequate radiotherapy.^{3-5,15}

Tumour-free margins

The importance of a tumour-free margin and the necessity to boost the tumour bed is controversial.^{15,17,18} Our policy is to achieve a macroscopically tumour-free margin and to boost the tumour bed. It is therefore important that the surgeon should palpate the inside of the wound for residual cancerous areas thoroughly. On occasion we have detected an unsuspected second tumour. We believe the surgeon should transect the specimen during surgery to judge whether the margins are free of tumour, to measure the diameter and to verify the centre of the tumour, which is usually eccentrically placed in the specimen. If the tumour-free area is marginal, a further excision can be done immediately and accurately. A further advantage is that we are then able to adjust the booster area to encompass the area at risk. We regard this as a major advantage of intra-operative brachytherapy. A disadvantage of transecting the tumour is the fact that the pathological assessment of inked margins, which is standard practice, is more difficult.¹⁷ We subject all patients referred after a diagnostic biopsy to re-excision biopsy to achieve the goal set out above.¹⁹

Axillary lymph node dissection

The extent and need for axillary lymph node dissection remain controversial.^{20,21} Our policy is to perform a complete axillary lymph node clearance, which ensures excellent local control and selects patients who qualify for supraclavicular irradiation. Axillary lymph node irradiation, with its associated morbidity, is thus not indicated.²² In our experience a recurrence at the apex of the axilla after partial axillary lymph node dissection is extremely difficult to control.

Almost 60% of our patients were lymph node-negative on pathological examination and could possibly have been managed without axillary lymph node dissection.²⁰ However, clinical examination of the axilla is inaccurate in 30% of patients and there are no diagnostic imaging methods available to demonstrate axillary lymph node involvement.²³ Axillary lymph node sampling is utilised by some authors as an indicator for full axillary lymph node clearance or irradiation of the axilla. In practice, all patients should undergo axillary lymph node clearance until the question of delayed axillary lymph node clearance is clarified in a prospective study.

Nine of our patients had clinically undiagnosed apical lymph node involvement, which explains the rationale behind the treatment at institutions such as the Netherlands Cancer Institute, which practises apical lymph node biopsy before definitive treatment. The morbidity associated with axillary lymph node clearance includes prolonged hospitalisation owing to axillary drainage, risk of oedema of the arm, greater oedema of the breast and risk of impaired shoulder function.^{20,22}

Attempts to reduce the period of seroma formation, i.e. late mobilisation of the shoulder, early removal of the drains with repeated aspiration and pressure bandages, and the use of fibrin glue have all been unsuccessful.²⁴

Irradiation

Iridium implant

The importance of irradiation of the breast as well as adequate dosage is emphasised by the high rates of recurrence reported in the US National Surgical Adjuvant Breast Protocol⁴ and Guy's Hospital²⁵ studies.

The data of Harris and Hellman¹⁵ emphasise the importance of both tumour excision and booster to the tumour bed. Their 6-year rate of local tumour control was 89% for patients who had undergone excisional biopsy compared with only 66% for patients who had not. The 6-year risk of a recurrence of the primary tumour was 12% for patients who had not received a boost compared with 6% for those who had.

As some others, we prefer giving the booster dosage by an ¹⁹²Ir implant at the time of surgery.¹⁹ The advantages of this technique are that needles are placed accurately under direct vision, the surgeon can identify suspect areas, dosage is accurately delivered, a single anaesthetic is required, hospitalisation is not prolonged, and overall treatment time is shorter in comparison with an external booster or delayed implant.

Initially we used polythene tubing as described by Paine²⁶ in our implants. Source geometry and therefore dosage distribution were very uneven. We therefore changed to the rigid needle and template technique. Templates were made to our specifications by our physics laboratory technicians. This technique ensures that the sources remain parallel and straight. The use of stainless-steel needles reduces the dosage by less than 2%, as calculated by our physicists. The needles and templates are held in position by lead crimps, which are always available and are simpler to use than many complicated devices. The implant causes minimal discomfort and is removed painlessly. An afterloading apparatus is commercially available but only 1 patient can be treated over a period of 2 days. This is impractical and not cost-effective in our situation.

We use the Paris system⁷ because of its flexibility and adaptability to individual clinical situations.²⁷ Therefore we are able to use single-plane implants in certain situations with insufficient breast tissue, such as the upper inner quadrant. Double-plane implants, which treat a larger volume, are possible in virtually all other situations. Care should be taken to deliver the implant dosage at least 5 mm from the skin surface in order to minimise skin reaction and fibrosis, which causes poor cosmesis.

The optimal dosage for the booster has not been established. Trials to establish the efficacy of higher and lower dosages are in progress.

External beam therapy

Dosage is limited to 2 Gy fractions.¹⁵ Increasing the daily dosage causes increased fibrosis with poor cosmesis. The skin dose is limited by the use of wedge or compensating filters, bolus is not used.

Where sternal or supraclavicular fields are treated, great care must be exercised to ensure that fields do not overlap. This causes marked fibrosis and poor cosmesis.

Local recurrence

We classify recurrent disease as: (i) a recurrence occurring within the booster area; (ii) a tumour occurring outside the booster area within the irradiated area — this may represent a true recurrence or another primary tumour; and (iii) a tumour occurring outside the irradiated area, which we consider a metastasis.

The discovery of a lump is equally traumatic for doctors and patients and both tend to overreact, accepting that it is malignant. Of 17 patients presenting with a recurrent lump, only 7 ultimately proved to have malignant disease in a review of 214 patients treated at Guy's Hospital, London.²⁸

The factors associated with a high incidence of local recurrence are:^{3,4,10,13,15,17} (i) positive axillary lymph nodes; (ii) residual tumour at the resection line; (iii) extensive carcinoma *in situ* in and surrounding the tumour; (iv) increasing size of the tumour; and (v) young age.

Scarring and fibrosis in the breast surrounding the tumour excision, and the presence of benign breast disease makes the recognition of recurrent carcinoma difficult.²⁷ The mammographic signs indicative of carcinoma are a mass lesion or new malignant-type microcalcifications. Other signs are nonspecific and common after treatment. Annual follow-up mammo-

graphy, starting 6 months after surgery, is strongly recommended.

On pathological examination, radiation-induced changes in normal breast tissue may be indistinguishable from carcinoma. Great care must be taken in the interpretation of fine-needle aspiration of recurrent lumps in the breast.²⁹ Histopathological confirmation, which could also be difficult, must be obtained before any treatment decision is made.³⁰ It is thus advisable that these patients are followed up by clinicians with experience of post-radiation changes. It must be emphasised that local recurrence in a conservatively treated breast does not have the same implication in terms of poor prognosis as local recurrence after mastectomy.¹⁵

The treatment of local recurrence depends on the site and extent of recurrence. We perform a mastectomy for recurrence within the booster area. Early resectable recurrent disease elsewhere may be treated by re-excision and an interstitial booster.¹⁵ Recurrence outside the treatment area is regarded as metastatic disease and should be treated accordingly.

Metastases

In reported randomised trials patients undergoing BCT have the same incidence of metastatic disease as those undergoing mastectomy.^{3,5}

Wound infection

Peri-operative brachytherapy *per se* has not been associated with wound infections or delayed wound healing in our experience.¹⁹ Early wound infection invariably occurred in patients receiving peri-operative CAF. We experienced the same problems in mastectomy patients receiving peri-operative CAF. In all our cases late wound infection was associated with persistent seroma formation following re-excision biopsy. These patients did not respond to antibiotics and wound drainage. Primary healing could only be obtained by excision of the cavity and surrounding indurated tissue. To prevent this complication, the drain must not be removed prematurely.

Conclusions

At Tygerberg Hospital a dramatic change in the treatment of stage I and II breast cancer has been observed during the past 5 years. BCT is now our accepted method of treatment.

We have demonstrated that by integrating sound surgical and radiotherapeutic principles, excellent local control and cosmesis can be achieved without compromising survival. In our experience intra-operative brachytherapy has many advantages without increasing postoperative morbidity. Used with care, peri-operative chemotherapy can be administered simultaneously.

Although not specifically evaluated in this study, it is apparent that the treatment options for stage I and stage II breast cancer are not widely known and BCT is not generally practised.

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